*Br. J. clin. Pharmac.* (1990), **30**, 501–510

# Disease modifying drugs for rheumatoid arthritis: yesterday's treatment today or today's treatment tomorrow?

T. PULLAR
Clinical Pharmacology Unit, Departments of Medicine and Pharmacology, University of Leeds, Leeds

## Introduction

In the past few years I have heard two statements which may be pertinent to the drug treatment of rheumatoid arthritis. The first of these, 'the effective treatment for rheumatoid arthritis is on the pharmacy shelf; all we must do is identify it' was a didactic statement by an eminent rheumatologist. The second statement, by a somewhat less eminent and more cynical individual, was, 'if we stopped all research over the next 5 years and expended the same energy in applying the knowledge we already have, patients would be better off'. I wish to explore the truth of these two statements with respect to potentially disease-modifying anti-rheumatoid drugs (DMARDs) and, in the process, to examine the past, current and future status of such therapy.

## Disease modifying anti-rheumatoid drugs (DMARDs)

DMARDs, also known as second line drugs, D-penicillamine-like drugs or slow-acting anti-rheumatoid drugs (SAARDs) are characterised by their ability to improve both routine clinical and laboratory indices of inflammation and probably also affect the outcome of the disease (i.e. retard structural damage to the joints). This is in contrast to non-steroidal anti-inflammatory drugs which affect clinical but not laboratory indices and have no beneficial effect on disease outcome (Table 1). Cytotoxic drugs, traditionally known as third line drugs, have similar properties and also fit into the category of DMARDs.

### *'Off the shelf' treatments for rheumatoid arthritis*

It is certainly true that most drugs which have some ability to alter disease activity and outcome in rheumatoid arthritis were introduced for other purposes. Intra-muscular gold was initially used for the treatment of tuberculosis. It was only similarities between tuberculosis and the condition which later became known as rheumatoid arthritis, and a belief that it too might be caused by a mycobacterium, which led Forestier (1929) to introduce gold thiopropanol sodium sulphonate for this condition. His initial success and the early UK experience gained in Leeds (Hartfall *et al.*, 1937a,b) was confirmed in the first double-blind placebo-controlled trial in rheumatology (Fraser, 1945) which was carried out in Glasgow. This was confirmed further by the Empire Rheumatism Council Study (1960). That controlled trials were felt necessary, may reflect the fact that, although a significant advance, gold was by no means a 'cure' for the disease. The use of injectable gold has evolved over the years from short courses to long-term treatment, but despite its use for most of this century we are little wiser than Forestier was as to how it produces its clinical effect.

Discovery of the anti-rheumatoid properties of antimalarials owed even more to serendipity. In 1951 a report was published of two patients with malaria treated by mepacrine in whom coincidental lupus erythematous improved (Page, 1951). This prompted further studies in connective tissue diseases, and the first published placebo controlled trials of chloroquine (Freedman, 1956) and hydroxychloroquine (Hamilton & Scott, 1962) in rheumatoid arthritis.

Penicillamine was first used clinically in 1956 in the treatment of Wilson's disease (Walshe, 1956). Because it could dissociate certain macroglobulins *in vitro* it was tried in rheumatoid arthritis, and was found to reduce the titre of rheumatoid factor. This finding, although it is now thought to be unrelated to its mode of action, led to a multicentre placebo-controlled trial which proved its efficacy (Multicentre Trial Group, 1973). The activity of penicillamine is

Correspondence: Dr T. Pullar, Clinical Pharmacology Unit, University Department of Medicine, The General Infirmary, Leeds LS1 3EX

**Table 1** Comparison of effects expected from non-steroidal anti-inflammatory drugs and disease modifying anti-rheumatoid drugs

| | *Non steroidal anti-inflammatory drugs (NSAIDs)* | *Disease modifying anti-rheumatoid drugs (DMARDs)* |
|---|---|---|
| Rate of onset of action | *hours–days* | *months* |
| Pain score | ↓ | ↓ |
| Articular index (count of tender joints) | ↓ | ↓ |
| Duration of morning stiffness | ↓ | ↓ |
| Hand grip strength | ↑ | ↑ |
| Erythrocyte sedimentation rate | – | ↓ |
| Plasma viscosity | – | ↓ |
| C-reactive protein | – | ↓ |
| Haemoglobin | – | ↑ |
| Platelet count | – | ↓ |
| Albumin | – | ↑ |
| Serum thiols | – | ↑ |
| Rate of radiological deterioration | – | ↓ |
| Rate of functional deterioration | – | ↓ |

now thought to be related to its possession of a thiol group, and for this reason tiopronin, a thiol containing compound used in Wilson's disease, and captopril, an ACE inhibitor which possesses a thiol group, were investigated and found to have 'disease modifying' activity (Martin *et al.*, 1984; Pasero *et al.*, 1982). Another ACE inhibitor, pentopril, which possesses no thiol group has been found to have no such activity using the 'Leeds patient model system' (Dixon *et al.*, 1982) which correlates changes in clinical parameters with changes in laboratory parameters (Bird *et al.*, 1990). In an attempt to investigate whether penicillamine acts via its metal chelating properties, another chelating agent used in Wilson's disease, trien, was tried in the Leeds patient model system but found ineffective (Dixon *et al.*, 1984).

Sulphasalazine was synthesised initially because it was thought that the combination of an anti-inflammatory and antibiotic might be beneficial in 'rheumatic polyarthritis' and ulcerative colitis (Svartz, 1942). The outcome of an open controlled trial comparing sulphasalazine with i.m. gold and 'no specific treatment' (Sinclair & Duthie, 1949), delayed its widespread use in rheumatology by over thirty years. However, this trial had a number of serious shortcomings. It had small numbers (20 patients per group), a smaller maintenance dose was used compared with earlier studies, all patients were initially hospitalised for at least 4 weeks (mean = 9 weeks) and in many patients assessments were carried out many months after cessation of therapy. This study found neither sulphasalazine nor gold (the 'positive control') to be any different from 'no specific treatment'. Despite these shortcomings and the results of another controlled study published the following year (Kuzell & Gardner, 1950) sulphasalazine fell into disrepute for the treatment of rheumatoid arthritis. It was reintroduced because of its structural similarity to dapsone, another effective 'off the shelf' drug first studied because of the similarities between rheumatoid arthritis and leprosy (McConkey *et al.*, 1976), and because both were effective in dermatitis herpetiformis. This open trial found it to be effective (McConkey *et al.*, 1978) and once again this resulted in a controlled trial which confirmed efficacy (Pullar *et al.*, 1983). Although Svartz's original hypothesis concerning the sulphonamide antibiotic may still explain its efficacy, the presence of 5-ASA seems to be of no relevance (Pullar *et al.*, 1985a). The efficacy of sulphasalazine and sulphapyridine has resulted in investigation of other antibiotics. Two open trials of rifampicin, an interesting choice in view of Forestier's original hypothesis, have disagreed concerning its efficacy (Cox *et al.*, 1989; McConkey & Situnayake, 1988). Ciprofloxacin, another broad spectrum antibiotic, appeared ineffective

in one open study (Mortiboy & Palmer, 1989). Although the efficacy of sulphapyridine has been confirmed (Neumann *et al.*, 1986) there have been conflicting reports on the efficacy of another sulphonamide sulphamethoxazole, (Ash *et al.*, 1986; Astbury *et al.*, 1986). This poses the question whether or not the efficacy of sulphapyridine is due to its antimicrobial effect. Another antimicrobial, in this case an anti-helminthic, whose use pre-dated the reintroduction of sulphasalazine was levamisole. It was tried initially in rheumatoid arthritis because of its immunomodulating effect. Despite controlled trials showing efficacy (Multicentre Study Group, 1978) it has fallen into disuse because of toxicity. Phenytoin, another drug known to alter immune function, has also been investigated in rheumatoid arthritis and found to improve clinical and especially laboratory parameters of inflammation, but apparently to a much lesser extent than sodium aurothiomalate (Richards *et al.*, 1987).

Stanozolol, an oral anabolic steroid with fibrinolytic activity, has also been shown to reduce disease activity in one controlled trial (Belch *et al.*, 1986). The rationale for its use was the finding of reduced fibrinolytic activity in patients with rheumatoid arthritis. Side effects, in particular virilisation, have again precluded long term use. Another anabolic steroid, nandrolone decanoate, is probably ineffective as a disease modifying agent (Bird *et al.*, 1987).

Haloperidol appeared promising in an open study (Grimaldi, 1981), perhaps due to its effect of stabilising platelet membranes. Thalidomide, which like dapsone also is useful in leprosy, has recently been investigated in an open fashion and appears to have disease modifying effects (Gutierrez-Rodriguez *et al.*, 1989). Cyclosporin A has been investigated intensively in rheumatoid arthritis. The general conclusion is that it does have disease modifying activity, but its usefulness is limited by its nephrotoxicity (Dougados *et al.*, 1988; Weinblatt *et al.*, 1987). Other 'off the shelf" drugs which have been investigated but found ineffective in rheumatoid arthritis include feverfew (Pattrick *et al.*, 1989), zinc sulphate (Dixon *et al.*, 1984), etidronate (Bird *et al.*, 1988a), pamidronate (Ralston *et al.*, 1989) and desferrioxamine (Polson *et al.*, 1986) whereas the retinoic acid derivative, etretinate, has been found to have some activity (Bird *et al.*, 1988b).

The 'cytotoxic drugs' azathioprine, methotrexate, and chlorambucil, were all introduced for the treatment of malignancy, but have proven effective in rheumatoid arthritis. However the dose regimens are often very different for rheumatoid arthritis. There has also been interest recently in the use of recombinant interferons in rheumatoid arthritis, but any beneficial effect seems to be slight (Cannon *et al.*, 1989). Finally, although Hensch had postulated the efficacy of an adrenal cortical hormone in rheumatoid arthritis before its isolation, it was not primarily for the treatment of rheumatoid arthritis that cortisone was produced (Weiss, 1989). Table 2 summarises the various 'off the shelf' drugs which have been investigated.

Thus the majority of established disease modifying agents were originally developed for other reasons, and many more 'off the shelf' drugs have been tested and found to have some activity.

### *Tailor made drugs*

Relatively few drugs have been designed specifically as DMARDs. The only example currently in routine use is auranofin, an oral gold compound which appears to have efficacy towards the lower end of the spectrum (Wright, 1984). A number of other drugs such as clobuzarit and pirinomide have been developed specifically as DMARDs but were never licensed because of problems with toxicity. Two drugs which were developed for the treatment of inflammatory arthritis and were generally regarded as non-steroidal anti-inflammatory drugs probably did have some disease modifying activity, namely fenclofenac (Nuki, 1983) and benoxaprofen (Anon, 1982). Both were withdrawn from the market because of toxicity. Currently a number of new drugs including romazarit, a close relative of clobuzarit, OM-8980 (Hanzeuer & Appelbaum, 1989) and timegadine (Egsmose *et al.*, 1988) are being investigated specifically as DMARDs.

### *'Off the shelf' treatments of the future*

Historically, therefore, the major advances and most of the clinical research in DMARD therapy have involved drugs already available for the treatment of other conditions. This is a cheap alternative to developing a new entity, with the attendant high risk of failure, for a fairly small therapeutic field. Treatments were not, however, plucked at random from the pharmacy shelf, but were chosen because known pharmacological effects suggested that they might alter processes thought important in the pathogenesis of rheumatoid arthritis at the time. It might appear with hindsight that the established efficacy of many of these drugs owes more to serendipity than science. However, we are even now ignorant of

**Table 2** 'Off the shelf' drugs which have been investigated for the treatment of rheumatoid arthritis

| | *Effective* | *Studies* | *Used in standard clinical practice* |
|---|---|---|---|
| sodium aurothiomalate | Yes | Blind *vs* placebo | Yes |
| D-penicillamine | Yes | Blind *vs* placebo | Yes |
| (hydroxy)chloroquine | Yes | Blind *vs* placebo | Yes |
| sulphasalazine | Yes | Blind *vs* placebo | Yes |
| methotrexate | Yes | Blind *vs* placebo | Yes |
| azathioprine | Yes | Blind *vs* placebo | Yes |
| cyclophosphamide | Yes | Blind *vs* placebo | Yes |
| captopril | Probably | * Open uncontrolled | No |
| pentopril | No | * Open uncontrolled | No |
| 5-ASA | No | Open *vs* sulphapyridine | No |
| sulphapyridine | Yes | Open *vs* 5-ASA (blind assessments) | No |
| rifampicin | Unresolved | Open uncontrolled | No |
| ciprofloxacin | Probably not | Open uncontrolled | No |
| sulphamethoxazole | Unresolved | Open *vs* placebo (observer blinded) * Open uncontrolled | No |
| levamisole | Yes | Blind *vs* placebo | No |
| phenytoin | Yes but relatively slight | Open *vs* gold | No |
| stanozolol | Yes | Blind *vs* placebo | No |
| nandrolone decanoate | No | Open *vs* placebo (observer blinded) | No |
| haloperidol | Probably | Open uncontrolled | No |
| thalidomide | Probably | Open uncontrolled | No |
| cyclosporin A | Yes | Blind *vs* placebo | No |
| γ-interferon | Yes but relatively slight | Blind *vs* placebo | No |
| pamidronate | No | Blind *vs* placebo | No |
| desferrioxamine | No | Open uncontrolled | No |
| dapsone | Yes | Open uncontrolled | No |
| trien | No | *Open uncontrolled | No |
| zinc sulphate | No | *Open uncontrolled | No |
| etretinate | Yes | *Open uncontrolled | No |
| etidronate | No | *Open uncontrolled | No |
| feverfew | No | Blind *vs* placebo | No |
| tiopronin | Yes | Blind *vs* penicillamine | No |

*Leeds patient model system.

the pathogenic process in rheumatoid arthritis. It is apparent that as our knowledge of the disease process grew, aspects which might be altered by drug treatment became apparent. Some of the drugs examined were already well established in the treatment of other conditions. Others had recently been developed, perhaps because of increasing knowledge of the nature of other diseases.

Further advances in our understanding of rheumatoid arthritis will be needed if we are to decide rationally which other drugs might prove useful. These drugs may already be available, or we may have to await their development related to increased knowledge in parallel areas of medicine, for example in the prevention of organ transplant rejection or the treatment of AIDS. We may therefore find effective DMARDs on the pharmacy shelf in the future, but it is likely that they are not there at present. Greater knowledge and understanding of the underlying disease process will be necessary however to enable us to identify drugs as promising. The fact that future treatments may well be 'off the shelf' rather than 'designer' does not therefore negate in any way the necessity for basic research into the pathogenesis of rheumatoid arthritis. On the contrary greater rewards may emerge from such research than might be expected if we confined ourselves to drugs developed specifically for rheumatoid arthritis.

## Research *vs* application

The second statement for discussion in relation to DMARDs is the suggestion that the next 5 years would be better spent utilising current knowledge clinically rather than on further research. This presupposes that we already have sufficient factual knowledge of the optimal use of current treatments, as opposed to conjecture or 'standard practice' on which clinical use of these drugs should be based. It assumes also that this knowledge is not being applied at present. Thirdly it assumes that the failure to apply this knowledge can be rectified by time and effort.

### *Current state of knowledge*

What do we *know* about second line or disease modifying drugs? By definition, when given to the right patients for 6 months or more, and provided they are tolerated, they cause symptomatic improvement and changes towards normal in laboratory indices of inflammation. There is a high drop out rate because of toxicity and because of failure to respond. With the possible exception of methotrexate there is a broad correlation between efficacy and toxicity. It seems very likely, considering recent papers by Borg *et al.* (1988) and Van der Heijde *et al.* (1989) that DMARDs do slow both radiological progression and functional deterioration. The first of these papers describes an intention to treat analysis in patients with early rheumatoid arthritis who were randomised to auranofin or placebo. After 2 years there were significant differences between the groups although more than 50% of placebo treated patients had started DMARDs, 28% of auranofin treated patients had changed treatment, and the mean delay in starting DMARD therapy in the placebo group was 8 months. Van der Heijde and her colleagues (1989) examined radiological progression during treatment with sulphasalazine and hydroxychloroquine for 1 year, and found that sulphasalazine significantly retarded radiological progression. The difference was maintained over the next 2 years despite changes in treatment (Van der Heijde *et al.*, 1990).

### *Current state of uncertainty*

Many aspects of treatment such as dosage schedules, monitoring schedules and the order of use of drugs owe much to collective experience and standard clinical practice. Unrealistic advice is sometimes given regarding dose schedules. For example the data sheet for penicillamine (Distamine) recommends that the 'minimum maintenance dose to achieve suppression of symptoms should be used'. In fact these drugs rarely suppress symptoms entirely. In practice the dose is often increased only until clinical improvement is achieved although there is evidence that higher doses may produce a greater response (Martin *et al.*, 1982a, b). Again, sulphasalazine appears to be more effective at doses higher than those generally used (Pullar *et al.*, 1985b). This difficulty is underlined by evidence that we do not yet know our expectations from the use of such drugs (Scott *et al.*, 1989), that different rheumatologists may have different expectations (Symmons *et al.*, 1989), and that even when we know what we want we cannot agree whether or not we have achieved it (Kirwan *et al.*, 1984).

Recently it has been argued that we should change our approach to the management of active rheumatoid arthritis from the so-called 'pyramid' approach which uses, in escalating order, drugs of increasing efficacy and toxicity when less effective treatments have proven unsatisfactory. The alternative approach is the 'step down

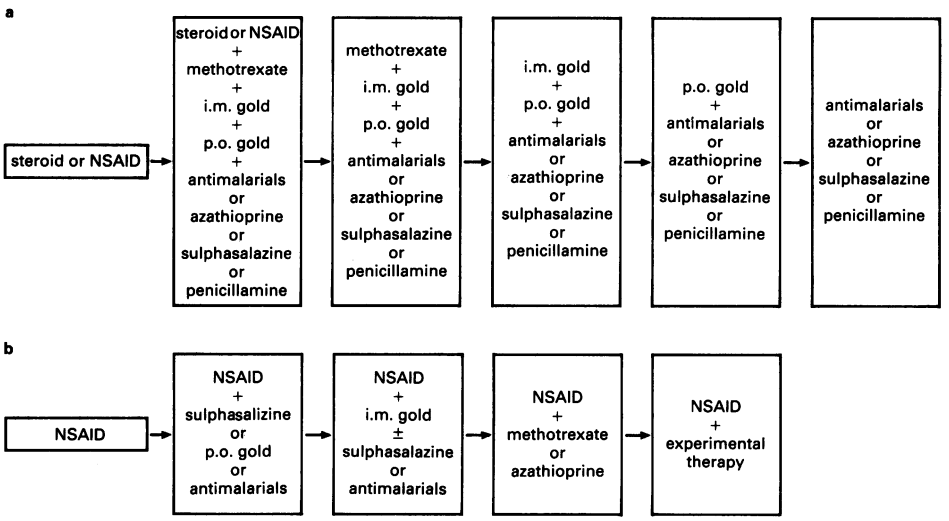


**Figure 1** a) 'Step down bridge approach', b) my own pyramid approach.

bridge' in which effective but potentially toxic drugs such as prednisolone and methotrexate are introduced early, in combination with other drugs such as sodium aurothiomalate, auranofin and antimalarials (or penicillamine or sulphasalazine). Subsequently the more potent drugs are withdrawn stepwise when disease control is achieved, but may be reintroduced at times of relapse (Healy & Wilske, 1989) (Figure 1). Such a regimen may expose patients unnecessarily to toxic drugs. The development of adverse effects such as leukopenia, thrombocytopenia, rash or oral ulceration would present a diagnostic nightmare, and could preclude the use of many valuable therapeutic agents in one fell swoop. The 'bridge' approach has been criticised recently by Hess & Luggan (1989).

With the traditional pyramid approach there is uncertainty about the best method of using these drugs in combination. It seems a sound principle to avoid use of two drugs when one will suffice. Almost all studies of combined therapy have been designed in a way which may result in many patients receiving two drugs unnecessarily. Many have compared drug A alone with drug A +B in combination from the outset, or have introduced drug B after a short period on drug A alone irrespective of response (Bunch *et al.*, 1984; Gibson *et al.*, 1986; Martin *et al.*, 1982a; Sievers & Hurri, 1963; Taggart *et al.*, 1987). Not surprisingly these study designs often show that combination treatment is superior. This outcome could occur without any synergistic or additive effect within individual patients. If we assume for example that 20% of the patient population are unresponsive to drug A, and a different 20% are unresponsive to drug B, then 96% of patients will respond to combined treatment even if drug A produces no additional benefit to drug B responders or *vice versa*. In another study either drug B or placebo were added in double-blind random fashion to the regimen of patients who showed a poor response to drug A alone (Martin *et al.*, 1982b). With this study design superiority of the combination would again hardly be surprising. The question of real clinical relevance is whether in cases of partial response drug B should be used instead of drug A, or should be added to drug A (Figure 2).

Another area of uncertainty in the clinical use

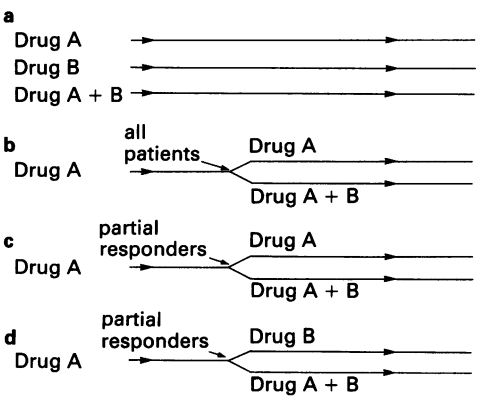


**Figure 2** Different designs for studying combination therapy. Only in design d) is superiority of the combination regimen likely to imply a synergistic or additive effect and answer a valid clinical question.

of DMARDs is which patients should receive them. Standard policy is to treat patients with active disease whose symptoms are not controlled by analgesics or non-steroidal anti-inflammatory drugs alone. Symptomatic response in this situation is independent of initial laboratory measures such as ESR (Pullar & Capell, 1986). The current trend is to start treatment earlier in the course of the disease (Spector *et al.*, 1988), and to treat patients with milder disease. With the advent of less toxic drugs such as sulphasalazine and auranofin this is a more acceptable option. The work of Borg *et al.* (1988) would certainly support earlier use. However there remains the counter-argument that earlier use and use in milder categories of disease may cause unnecessary drug toxicity.

There is no general agreement on the order of use of drugs in the 'pyramid' approach, although 'milder' less toxic drugs such as the antimalarials or sulphasalazine are often used first. There is no accepted rank order of these drugs as regards efficacy, with authors disagreeing to some extent in their semi-objective analysis of the literature (Furst, 1990; Pullar, 1990). It is however probably accepted that sodium aurothiomalate is the most effective (and toxic) of the second line drugs excluding the cytotoxic agents.

Why is there so much uncertainty about the clinical use of these drugs? Although they are doubtlessly effective, the mean improvement in inflammatory parameters observed is only about 50% (Scott *et al.*, 1990) and this varies from one parameter to another. Thus large numbers are required even to demonstrate a difference between active drug and placebo. To detect a difference of 10 mm $h^{-1}$ fall in ESR between two drugs with an $\alpha = 0.05$ and a $1 - \beta = 0.9$, the sample size required would be 400 patients completing a 6 month study. The drop-out rate is usually about 40%. It has been stated that prednisone and methotrexate are the only two medications which do not require a statistician to prove their efficacy (Healy & Wilske, 1989), although many British rheumatologists might dispute the truth of this for methotrexate. From a pragmatic point of view, however, the relative efficacy of these drugs may be of little importance as the discontinuation rate is such that most patients will require more than one agent over the course of their disease. The final choice of agent is therefore likely to be dictated by the tolerability and efficacy in a particular individual (Pullar *et al.*, 1985c; Situnayake *et al.*, 1987).

Further reasons for the poor state of knowledge regarding the clinical use of these drugs are the 'softness' of many measurements of short-term efficacy, and the length of time required to see convincing effects on outcome. Pronounced early symptomatic responses make prolonged conventional placebo controlled comparisons to examine outcome measurements, such as radiological progression virtually impossible, and explain why there has been so much uncertainty about the effect of these drugs on radiological progression (Pullar *et al.*, 1984; Pullar & Capell, 1985).

### *Improved application of current knowledge*

Despite the uncertainties surrounding the use of these drugs some changes in practice based on our current knowledge would probably improve the lot of the patient. Earlier referral to a rheumatologist may lead to earlier and more effective use of DMARDs in patients with active disease. Currently the median time to referral is 20 months, and the median time to DMARD therapy is a further 5 months (Spectör *et al.*, 1988). Assuming a waiting time of about 2 months before clinic attendance, then rheumatologists start DMARD therapy very soon after first seeing the patient. Better clinical documentation of objective and semi-objective measures of inflammation, and perhaps of outcome, may identify those patients who require further therapeutic intervention earlier and more effectively. A large proportion of poor responders to penicillamine are known to have poor compliance (Pullar *et al.*, 1988). If compliance with these drugs was improved, response and outcome might be enhanced.

However it would be wrong to assume that we need merely apply current knowledge to the clinical use of these agents to make major changes in the effect of treatment. One could argue that opportunities to improve practice are wasted when these drugs are used outwith carefully organised controlled clinical trials which aim to define their optimal use.

## Conclusions

One does not need a statistician to prove the efficacy of prednisolone, at least in terms of short term benefit. New 'off the shelf' or 'designer' drugs are needed with this degree of short term benefit coupled to a greater beneficial effect on long-term outcome and less toxicity. Thus more basic research is needed to produce more effective agents, and more clinical research and evaluation is also necessary to allow more effective use of the relatively ineffective armamentareum currently available.

I should like to thank Dr H. A. Capell and Dr M. P. Feely for their comments on the manuscript and Mrs M. E. Smith for typing it.

## References


Anon (1982). Benoxaprofen. *Br. med. J.*, **285**, 459–460.

Ash, G., Baker, R., Rajapakse, C. & Swinson, D. R. (1986). Study of sulphamethoxazole in rheumatoid arthritis. *Br. J. Rheumatol.*, **25**, 285–287.

Astbury, C., Hill, J. & Bird, H. A. (1986). Cotrimoxazole in rheumatoid arthritis. *Br. J. Rheumatol.*, **26**, (Abstract Suppl. 1), 9.

Belch, J. J. F., Madhok, R., McArdle, B., McLaughlin, K., Kluft, C., Forbes, C. D. & Sturrock, R. D. (1986). The effect of increasing fibrinolysis in patients with rheumatoid arthritis: a double blind study of stanozolol. *Quart. J. Med.*, **58**, 19–27.

Bird, H. A., Burkinshaw, L., Pearson, D., Atkinson, P. J., Leatham, P. A., Hill, J., Raven, A. & Wright, V. (1987). A controlled trial of nandrolone decanoate in the treatment of rheumatoid arthritis in postmenopausal women. *Ann. Rheum. Dis.*, **46**, 237–243.

Bird, H. A., Hill, J., Sitton, N. G., Dixon, J. S. & Wright, V. (1988a). A clinical and biochemical assessment of etidronate sodium in patients with active rheumatoid arthritis. *Clin. Rheumatol.*, **7**, 91–94.

Bird, H. A., Hill, J. S., Sitton, N. G., Dixon, J. S. & Wright, V. (1988b). A clinical and biochemical evaluation of etretinate in rheumatoid arthritis. *Rheumatol. Int.*, **8**, 55–59.

Bird, H. A., Le Gallez, P., Dixon, J. S., Catalano, M. A., Traficante, A., Lianw, L., Sussman, H., Rotman, H. & Wright, V. (1990). A clinical and biochemical assessment of a non-thiol ACE inhibitor (pentopril; CGS–13945) in active rheumatoid arthritis. *J. Rheumatol.*, **17**, 603–608.

Borg, G., Allander, E., Lund, B., Berg, E. & Brodin, U. (1988). Auranofin improves outcome in early rheumatoid arthritis: results from a 2-year, double-blind, placebo controlled study. *J. Rheumatol.*, **15**, 1747–1754.

Bunch, T. W., O'Duff, J. D., Tomkins, R. B. & O'Fallon, W. M. (1984). *Arthritis & Rheumatism*, **27**, 267–276.

Cannon, G. W., Pincus, S. H., Emkey, R. D., Denes, A., Cohen, S. A., Wolfe, F., Saway, P. A., Jaffer, A. M., Weaver, A. L., Cogen, L. & Schindler, J. D. (1989). Double-blind trial of recombinant γ-interferon versus placebo in the treatment of rheumatoid arthritis. *Arthritis & Rheumatism*, **32**, 964–973.

Cox, N. L., Maddison, M. C. & Maddison, P. J. (1989). Rifampicin and isoniazid do not work in early RA. *Br. J. Rheumatol.*, **28** (Abstract Suppl. 1), 23–24.

Dixon, J. S., Bird, H. A., Pickup, M. E. & Wright, V. (1982). A human model screening system for the detection of specific anti-rheumatic activity. *Sem. Arthritis Rheum.*, **12**, 185–190.

Dixon, J. S., Bird, H. A., Surrall, K. E., Sitton, N. G. & Wright, V. (1984). A comparison of therapies which may influence trace metals in rheumatoid arthritis. *Clin. Rheumatol.*, **3**, 451–458.

Dougados, M., Awada, H. & Amor, B. (1988). Cyclosporin in rheumatoid arthritis: a double blind, placebo controlled study in 52 patients. *Ann. Rheum. Dis.*, **47**, 127–133.

Egsmose, C., Lund, B. & Andersen, R. B. (1988). Timegadine: more than a non-steroidal for the treatment of rheumatoid arthritis. A controlled, double-blind study. *Scand. J. Rheumatol.*, **17**, 103–111.

Empire Rheumatism Council (1960). Gold therapy in rheumatoid arthritis: report of a multicentre controlled trial. *Ann. Rheum. Dis.*, **20**, 315–354.

Forestier, J. (1929). L'aurotherapie dan les rheumatismes chroniques. *Bull. Soc. Med. Hop. Paris*, **53**, 323–327.

Fraser, T. N. (1945). Gold treatment in rheumatoid arthritis. *Ann. Rheum. Dis.*, **4**, 71–75.

Freedman, A. (1956). Chloroquine and rheumatoid arthritis: a short term controlled trial. *Ann. Rheum. Dis.*, **15**, 251–256.

Furst, D. E. (1990). Rational use of disease-modifying anti-rheumatic drugs. *Drugs*, **39**, 19–37.

Gibson, T., Emery, P., Armstrong, R., Crisp, A. & Panayi, G. (1986). Combined chloroquine and d-penicillamine in rheumatoid arthritis – better or worse? *Br. J. Rheumatol.*, **25**, 114–115.

Grimaldi, M. G. (1981). Long-term low dose haloperidol treatment in rheumatoid patients: effects on serum sulphydryl levels, technetium index, ESR and clinical response. *Br. J. clin. Pharmac.*, **12**, 579–581.

Gutierrez-Rodriguez, O., Starusta-Bacal, P. & Gutierrez-Montes, O. (1989). Treatment of refractory rheumatoid arthritis – the thalidomide experience. *J. Rheumatol.*, **16**, 158–163.

Hamilton, E. B. D. & Scott, J. T. (1962). Hydroxychloroquine sulfate (plaquenil) in rheumatoid arthritis. *Arthritis Rheum.*, **5**, 502–512.

Haunzeur, J. P. & Appelboom, T. (1989). Double-blind placebo-controlled study of OM-8980 in rheumatoid arthritis. *Rheumatol. Int.*, **9**, 71–76.

Hartfall, S. J., Garland, H. E. & Goldie, W. (1937a). Gold treatment of arthritis; a review of 900 cases. *Lancet*, **ii**, 784–788.

Hartfall, S. J., Garland, H. E. & Goldie, W. (1937b). Gold treatment of arthritis; a review of 900 cases. *Lancet*, **ii**, 838–842.

Healy, L. A. & Wilske, K. R. (1989). Reforming the pyramid. A plan for treating rheumatoid arthritis in the 1990s. *Rheumatic Disease Clinics of North America*, **15**, 615–619.

Hess, E. V. & Luggen, M. E. (1989). Remodelling the pyramid – A concept whose time has not yet come. *J. Rheumatol.*, **16**, 1175–1176.

Kirwan, J. R., Chaput de Saintong, D. M., Joyce, C. R. B. & Currey, H. L. F. (1984). Clinical judgement in rheumatoid arthritis III. British rheumatologist's judgements of 'change in response to therapy'. *Ann. Rheum. Dis.*, **43**, 686–694.

Kuzell, W. K. & Gardner, G. H. (1950). Salicylazosulfapyridine (salazopyrin or azopyrin) in rheumatoid arthritis and experimental polyarthritis.

*California Medicine*, **73**, 476–480.

Martin, M., Dixon, J., Hickling, P., Bird, H. A., Golding, J. & Wright, V. (1982a). A combination of d-penicillamine and hydroxychloroquine in the management of rheumatoid arthritis. *Ann. Rheum. Dis.*, **41**, 208.

Martin, M., Sitton, N., Dixon, J., Hickling, P., Golding, J. & Wright, V. (1982b). Penicillamine failures – what can be done? *Ann. Rheum. Dis.*, **41**, 631–632.

Martin, M. F. R., Surrall, K. E., McKenna, F., Dixon, J. S., Bird, H. A. & Wright, V. (1984). Captopril: a new treatment for rheumatoid arthritis? *Lancet*, **i**, 1325–1327.

McConkey, B., Amos, R. S., Butler, R. A., Crockson, R. A., Crockson, A. P. & Walsh, L. (1978). Salazopyrine in rheumatoid arthritis. *Agents & Actions*, **8**, 438–441.

McConkey, B., Davies, P., Crockson, R. A., Crockson, A. P., Butler, M. & Constable, T. J. (1976). Dapsone in rheumatoid arthritis. *Rheumatol. Rehab.*, **15**, 230–234.

McConkey, B. & Situnayake, D. (1988). Effects of rifampicin with and without isoniazid in rheumatoid arthritis. *J. Rheumatol.*, **15**, 46–50.

Mortiboy, D. & Palmer, R. G. (1989). Ciprofloxacin and rheumatoid arthritis – lack of effect. *Br. J. Rheumatol.*, **28**, 272.

Multicentre Study Group (1978). Levamisole in rheumatoid arthritis. A randomised double-blind study comparing 2 dosage regimes of levamisole with placebo. *Lancet*, **ii**, 1007–1012.

Multicentre Trial Group (1973). Controlled trial of D(-) penicillamine in severe rheumatoid arthritis. *Lancet*, **i**, 275–280.

Neumann, V. C., Taggart, A. J., Le Gallez, P., Astbury, C., Hill, J. & Bird, H. A. (1986). A study to determine the active moiety of sulphasalazine in rheumatoid arthritis. *J. Rheumatol.*, **13**, 285–287.

Nuki, G. (1983). Non-steroidal analgesic and anti-inflammatory agents. *Br. med. J.*, **287**, 39–43.

Pasero, G., Pellegrini, P., Ambanelli, U., Gompi, M. L., Colamussi, V., Ferraccioli, G., Barbieri, P., Mazzoni, M. R., Menegale, G. & Trippi, D. (1982). Controlled multicenter trial of tiopronin and d-penicillamine for rheumatoid arthritis. *Arthritis & Rheumatism*, **25**, 923–929.

Page, F. (1951). Treatment of lupus erythematosus with mepacrine. *Lancet*, **ii**, 755–758.

Pattrick, M., Heptinstall, S. & Doherty, M. (1989). Feverfew in rheumatoid arthritis: a double blind placebo-controlled study. *Ann. Rheum. Dis.*, **48**, 547–549.

Polson, R. J., Jawad, A. S. M., Bomford, A., Berry, H. & Williams, R. (1986). Treatment of rheumatoid arthritis with desferrioxamine. *Quart. J. Med.*, **61**, 153–1158.

Pullar, T., Hunter, J. A. & Capell, H. A. (1983). Sulphasalazine in rheumatoid arthritis: a double blind comparison of sulphasalazine with placebo and sodium aurothiomalate. *Br. med. J.*, **287**, 1102–1104.

Pullar, T., Hunter, J. A. & Capell, H. A. (1984). Does second line therapy affect the radiological progression of rheumatoid arthritis? *Ann. Rheum. Dis.*, **43**, 18–23.

Pullar, T. & Capell, H. A. (1985). A rheumatological dilemma: is it possible to alter the course of rheumatoid arthritis? Can we answer the question? *Ann. Rheum. Dis.*, **44**, 134–140.

Pullar, T., Hunter, J. A. & Capell, H. A. (1985a). Which is the active component of sulphasalazine in rheumatoid arthritis? *Br. med. J.*, **290**, 1535–1538.

Pullar, T., Hunter, J. A. & Capell, H. A. (1985b). Sulphasalazine in the treatment of rheumatoid arthritis: relationship of dose and serum levels to efficacy. *Br. J. Rheumatol.*, **24**, 269–276.

Pullar, T., Hunter, J. A., & Capell, H. A. (1985c). Second line therapy in rheumatoid arthritis – A four year prospective study. *Clin. Rheumatol.*, **4**, 133–142.

Pullar, T. & Capell, H. A. (1986). Selection of suitable patients for second line therapy in rheumatoid arthritis. *Br. J. Rheumatol.*, **25**, 276–281.

Pullar, T., Peaker, S., Martin, M. F. R., Bird, H. A. & Feely, M. P. (1988). The use of a pharmacological indicator to investigate compliance in patients with a poor response to antirheumatic therapy. *Br. J. Rheumatol.*, **27**, 381–384.

Pullar, T. (1990). Decision making in the choice of second line agents. Europe/UK. In *Second line agents in the treatment of arthritis*, eds Dixon, J. S. & Furst, D. E. New York: Marcel Dekker. (in press).

Ralston, S. H., Hacking, L., Willocks, L., Bruce, F. & Pitkeathly, D. A. (1989). Clinical, biochemical and radiographic effects of aminohydroxypropylidene biphosphate treatment in rheumatoid arthritis. *Ann. Rheum. Dis.*, **48**, 396–399.

Richards, I. M., Fraser, S. M., Hunter, J. A. & Capell, H. A. (1987). Comparison of phenytoin and gold as second line drugs in rheumatoid arthritis. *Ann. Rheum. Dis.*, **46**, 667–669.

Scott, D. L., Spector, T. D., Pullar, T. & McConkey, B. (1989). What should we hope to achieve when treating rheumatoid arthritis? *Ann. Rheum. Dis.*, **48**, 256–261.

Scott, D. L., Dacre, J. E., Greenwood, A., Treasure, L. & Huskisson, E. C. (1990). Can we develop single response criteria for slow acting antirheumatic drugs. *Ann. Rheum. Dis.*, **49**, 196–198.

Sievers, K. & Hurri, L. (1963). Combined therapy of rheumatoid arthritis with gold and chloroquine. Evaluation of therapeutic effect. *Acta med. Scand.*, **9**, 48–52.

Sinclair, R. J. G. & Duthie, J. J. R. (1949). Salazopyrin in the treatment of rheumatoid arthritis. *Ann. Rheum. Dis.*, **8**, 226–231.

Situnayake, R. D., Grindulis, K. A. & McConkey, B. (1987). Long term treatment of rheumatoid arthritis with sulphasalazine, gold or penicillamine: a comparison using life-table methods. *Ann. Rheum. Dis.*, **46**, 177–183.

Spector, T. D., Thompson, P. W., Evans, S. J. W. & Scott, D. L. (1988). Are slow-acting antirheumatic drugs being given earlier in rheumatoid arthritis? *Br. J. Rheumatol.*, **27**, 498–499.

Svartz, N. (1942). Salazopyrin, a new sulfanilamide

preparatation. *Acta med. Scand.*, **110**, 577–598.

Symmons, D. P. M., Pullar, T., Scott, D. L., Coulton, B. L., Hill, J. & Studnicka, A. (1989). Second-line drug therapy – what constitutes a satisfactory response? *Br. J. Rheumatol.*, **28** (Abstract Suppl. 2), 117–118.

Taggart, A. J., Hill, J., Astbury, C., Dixon, J. S., Bird, H. A. & Wright, V. (1987). Sulphasalazine alone or in combination with d-penicillamine in rheumatoid arthritis. *Br. J. Rheumatol.*, **26**, 32–36.

Van der Heijde, D. M., Van Riel, P. L., Nuver-Swart, H. H., Gribnau, F. W. & van de Putte, L. B. (1989). Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. *Lancet*, **i**, 1036–1038.

Van der Heijde, D. M. F. M., van Riel, P. L., Nuver-Swart, H. H. & van de Putte, L. B. A. (1990). Sulphasalazine versus hydroxychloroquine in rheumatoid arthritis: 3-year follow-up. *Lancet*, **i**, 539.

Walshe, J. M. (1956). Penicillamine, a new oral therapy for Wilson's disease. *Am. J. Med.*, **21**, 487–495.

Weinblatt, M. E., Coblyn, J. S., Fraser, P. A., Anderson, R. J., Spragg, J., Trentham, D. E. & Austin, K. E. (1987). Cyclosporin A treatment of refractory rheumatoid arthritis. *Arthritis & Rheumatism*, **30**, 11–17.

Weiss, M. W. (1989). Corticosteroids in rheumatoid arthritis. *Seminars in Arthritis & Rheumatism*, **19**, 9–21.

Wright, V. (1984). Oral gold for rheumatoid arthritis. *Br. med. J.*, **289**, 858–859.

*(Received 23 April 1990, accepted 11 June 1990)*